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Abstract: **OBJECTIVE:** In 1999 we lowered the prostate-specific antigen (PSA) threshold for prostate biopsy at our institution from 4 to 2.5 ng/ml. The aim of this study was to compare the differences in tumor characteristics of the detected prostate cancers (PCAs) and the detection rate for the two different PSA thresholds and to evaluate if lowering the threshold was justified by any of the detected differences. **PATIENTS AND METHODS:** We retrospectively analyzed the records of all patients who underwent an 8-core prostate biopsy between January 1999 and December 2004 and had a PSA between 2.5 and 10 ng/ml. Patients with a PSA between 2.5 and 4 ng/ml (group 1, n = 214, mean age 62.0 years) were compared to patients whose PSA was between 4 and 10 ng/ml (group 2, n = 292, mean age 63.2 years). Patients who were older than 75 years or had a suspicious rectal examination were excluded from this study. **RESULTS:** Overall, we detected 120 cancers in 506 patients (cancer yield 23.7%). The cancer yield in group 1 was significantly lower than in group 2 (17 vs. 28%, $p < 0.01$). In group 1 significantly less Gleason score ≥ 7 ($p = 0.04$) and significantly more potentially insignificant cancers ($p = 0.03$) were identified. In 80 patients who subsequently underwent radical prostatectomy, final pathology revealed no significant differences between the two PSA groups with regard to high pT stages, Gleason score ≥ 7 PCA or positive surgical margins, respectively. The difference in the absolute risk of being diagnosed with high-grade PCA between a PSA threshold of 2.5 ng/ml and a PSA threshold of 4 ng/ml was 1%. **CONCLUSION:** Lowering the PSA threshold for prostate biopsy from 4 to 2.5 ng/ml results in a substantial increase in the number of men who undergo biopsy and may result in an increased detection of potentially insignificant cancers. If total PSA alone is used to determine the need for prostate biopsy, the disadvantages of this lower threshold probably outweigh its potential benefits.

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Lowering the PSA Threshold for Prostate Biopsy from 4 to 2.5 ng/ml: Influence on Cancer Characteristics and Number of Men Needed to Biopsy

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Key Words

Prostate biopsy · Prostate cancer · Prostate-specific antigen · Prostate-specific antigen threshold

Abstract

Objective: In 1999 we lowered the prostate-specific antigen (PSA) threshold for prostate biopsy at our institution from 4 to 2.5 ng/ml. The aim of this study was to compare the differences in tumor characteristics of the detected prostate cancers (PCAs) and the detection rate for the two different PSA thresholds and to evaluate if lowering the threshold was justified by any of the detected differences. **Patients and Methods:** We retrospectively analyzed the records of all patients who underwent an 8-core prostate biopsy between January 1999 and December 2004 and had a PSA between 2.5 and 10 ng/ml. Patients with a PSA between 2.5 and 4 ng/ml (group 1, n = 214, mean age 62.0 years) were compared to patients whose PSA was between 4 and 10 ng/ml (group 2, n = 292, mean age 63.2 years). Patients who were older than 75 years or had a suspicious rectal examination were excluded from this study. **Results:** Overall, we detected 120 cancers in 506 patients (cancer yield 23.7%). The cancer yield in group 1 was significantly lower than in group 2 (17 vs. 28%,

p < 0.01). In group 1 significantly less Gleason score ≥ 7 (p = 0.04) and significantly more potentially insignificant cancers (p = 0.03) were identified. In 80 patients who subsequently underwent radical prostatectomy, final pathology revealed no significant differences between the two PSA groups with regard to high pT stages, Gleason score ≥ 7 PCA or positive surgical margins, respectively. The difference in the absolute risk of being diagnosed with high-grade PCA between a PSA threshold of 2.5 ng/ml and a PSA threshold of 4 ng/ml was 1%. **Conclusion:** Lowering the PSA threshold for prostate biopsy from 4 to 2.5 ng/ml results in a substantial increase in the number of men who undergo biopsy and may result in an increased detection of potentially insignificant cancers. If total PSA alone is used to determine the need for prostate biopsy, the disadvantages of this lower threshold probably outweigh its potential benefits.

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Introduction

Over the last decade many centers have lowered their prostate-specific antigen (PSA) threshold for prostate biopsy to <4 ng/ml in order to detect more prostate cancers

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Table 1. Characteristics of men undergoing prostate biopsy by preinterventional PSA

	Group 1 PSA 2.5–4 ng/ml	Group 2 PSA 4–10 ng/ml	p value
Number of patients	214	292	
Mean age (SD, range)	62.0 (6.7, 44–75)	63.2 (6.9, 43–75)	0.05
Mean PSA (range)	3.2 (2.5–3.98)	6.1 (4.0–9.82)	<0.01
Mean prostate volume (range)	32.8 (13–100)	43.8 (13–300)	<0.01

(PCAs) at an organ-confined stage and thus possibly to improve cure rates [1, 2]. This measure, however, increases the number of men undergoing prostate biopsies substantially. The majority of these men are unnecessarily exposed to the morbidity and anxiety associated with the procedure [3]. Additionally, lowering PSA thresholds may lead to the detection of more clinically insignificant cancers and may further accentuate the problem of over-treatment [4, 5]. On the other hand, there is a debate whether PSA at low values even correlates with the risk of PCA [6]. Therefore, the optimal PSA cut-off to prompt a prostate biopsy, as well as a variety of other parameters to improve the performance of the PSA test, are of considerable current interest [7, 8].

In 1999 we lowered the PSA threshold for prostate biopsy at our institution from 4 to 2.5 ng/ml. The aims of the present analysis were: (1) to compare the differences in the tumor characteristics of the detected PCAs between the different PSA thresholds and (2) to report the differences in cancer detection rate and thus to estimate the number of men needed to biops to detect additional high-grade PCA in the PSA range 2.5–4 ng/ml.

Patients and Methods

We retrospectively analyzed the records of all patients who underwent an 8-core transrectal ultrasound-guided prostate biopsy in our department between January 1999 and December 2004. Our patients are typically men from a non-PSA-screened population. They were either referred to our department specifically for a prostate check-up that included a PSA test or had their PSA tested after informed consent during a urologic evaluation for other causes. For the purpose of this study we excluded patients who were older than 75 years and patients with a PSA value >10 or <2.5 ng/ml. Similarly, we excluded patients with a suspicious rectal examination because they would have undergone a prostate biopsy regardless of their PSA. In case we detected no PCA in the initial biopsy we routinely repeated the prostate biopsy after 4–6 weeks. We defined two groups of men according to the PSA value that triggered the first biopsy: men with a PSA between 2.5 and 4.0 ng/ml (group 1) and men with a PSA between 4 and 10 ng/ml (group 2).

We used the following five definitions throughout the analyses: (1) Patients with a positive (first or second) biopsy were classified as cancer-positive and patients with two consecutive negative biopsies were classified as cancer-negative. (2) Patients who were cancer-negative after the first biopsy and had no second biopsy were not end-classified for their cancer status and excluded from analysis of cancer-related outcomes (fig. 1). We compared patient variables of men who were not end-classified with men who were end-classified for their cancer status. (3) Potentially insignificant cancers were defined according to the pretreatment criteria of Carter et al. [9] to predict the presence of small-volume cancers. (4) High-grade PCA was defined as Gleason score ≥ 7 cancer. (5) Low pT categories were defined as pT2a–c, and advanced categories from pT3a upwards.

We compared the two patient groups for the total cancer yield, biopsy Gleason scores, and cancer volume in biopsy cores (more versus less than 50% cancer per biopsy core). In patients who underwent radical prostatectomy, we additionally compared the two groups with regard to positive surgical margins, final Gleason score, and pT staging. To test for differences between groups we used the t test for continuous variables and either the χ^2 test or the Fisher's exact test for categorical variables. We used logistic regression models to assess: (1) the association between cancer (dependent variable, yes/no) and PSA level with adjustment for age and prostate volume; (2) the association between Gleason score ≥ 7 cancers (dependent variable, yes/no) and PSA level with adjustment for age; (3) the association between potentially insignificant cancers (dependent variable, yes/no) and PSA level with adjustment for age. Statistical analyses were performed using SPSS version 12.0.1 (SPSS, Inc., Chicago, Ill., USA).

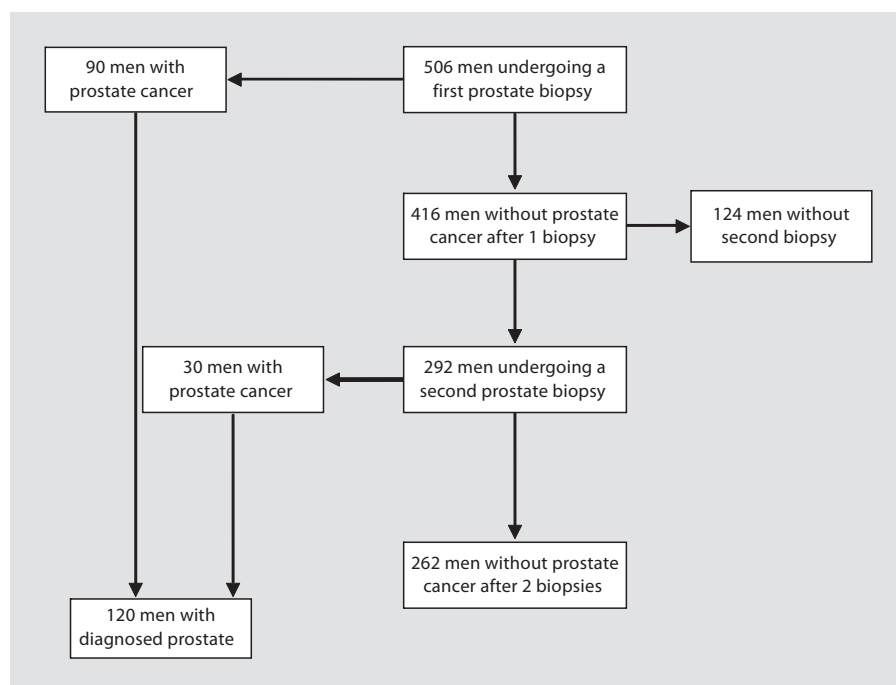
Results

A total of 506 patients met the inclusion criteria and the results of 798 prostate biopsies that were performed on these patients could be analyzed. Group 1 (PSA 2.5–4 ng/ml) consisted of 214 patients and group 2 (PSA 4–10 ng/ml) consisted of 292 patients. The median age was 63 years (range 43–75); patient characteristics are summarized in table 1. We detected 120 cancers in 506 patients, accounting for an overall cancer yield of 23.7% whereas the cancer yield for the first and second biopsy was 17.8 and 10.3%, respectively. There was no significant difference with respect to distribution of age categories

Table 2. Pathological characteristics of biopsy-detected PCA in the two PSA groups

	Group 1 PSA 2.5–4 ng/ml	Group 2 PSA 4–10 ng/ml	Relative risk (group 1 vs. group 2) (95% CI; p value)
Number of patients	214	292	
Cancer yield (%)	37/214 (17)	83/292 (28)	0.61 (0.43–0.86; $p < 0.01$)
Cancer volume in biopsy cores $\geq 50\%$ (%)	2/37 (5.4)	9/83 (10.8)	0.50 (0.11–2.20; $p = 0.5$)
Gleason score ≥ 7 (%)	4/37 (10.8)	24/83 (28.9)	0.37 (0.14–1.00; $p = 0.04$)
Potentially insignificant cancers ¹	5/24 (20.8)	3/69 (4.3)	4.79 (1.24–18.6; $p = 0.03$)

¹ Pretreatment criteria completely available for 93 patients with PCA (24 patients in group 1 and 69 patients in group 2).

**Fig. 1.** Study flow.

or PSA categories at first biopsy between patients without cancer end classification ($n = 124$) and patients with cancer end classification ($n = 382$).

The cancer yield was significantly lower in group 1 than in group 2 (17 vs. 28%, $RR = 0.61$, 95% $CI = 0.43–0.86$, $p < 0.01$). In the lower PSA group significantly less high-grade PCAs were detected than in the higher PSA group ($p = 0.04$). However, significantly more potentially insignificant cancers were identified in the lower PSA group ($p = 0.03$). Further characteristics of the detected PCAs in the two PSA groups are shown in table 2.

In the 80 patients who subsequently underwent radical prostatectomy, final pathology revealed no significant

differences between the two PSA groups with regard to the percentage of high pT categories, the percentage of patients with high-grade PCA or the percentage of patients with a positive surgical margin (table 3).

A logistic regression model restricted to the 382 patients who were end-classified with regard to their cancer status showed a significant positive association between cancer and higher PSA levels with an age- and prostate volume-adjusted odds ratio of 1.14 (95% $CI = 1.00–1.31$) per 1 ng/ml increase in PSA. Odds ratios to detect potentially insignificant cancer and high-grade PCA in group 1 relative to group 2 were 2.55 (95% $CI = 0.60–10.9$, $p = 0.21$) and 0.24 (95% $CI = 0.08–0.71$, $p = 0.01$), respectively.

Table 3. Tumor characteristics of men undergoing radical prostatectomy

	Group 1 PSA 2.5–4 ng/ml	Group 2 PSA 4–10 ng/ml	p value
Number of patients	27	53	
Gleason score ≥ 7 , n (%)	7 (25.9)	20 (37.7)	0.33
$\geq pT3$, n (%)	2 (7.7)*	5 (9.4)	0.99
Positive surgical margins, n (%)	4 (14.8)	7 (13.5)**	0.99

Data available for 26 patients (*) and 52 patients (**).

With a PSA threshold of 4 ng/ml, 24 out of 382 patients (6.3%) were identified with high-grade PCA. By lowering the threshold to 2.5 ng/ml, an additional 4 patients were detected for a total of 28 out of 382 patients (7.3%). This results in an absolute risk difference of 1% between the two thresholds. This difference was found to be statistically insignificant in our study population (95% CI = -2.5 to 4.6%).

Discussion

The positive association between rising PSA values and PCA detection that we found in our study is in accordance with the data from the first screening round of the European Randomized Study of Screening for Prostate Cancer (ERSPC) and with the Prostate Cancer Prevention Trial (PCPT) [10–12]. In both studies, rising PSA was positively associated with the risk of cancer detection. In contrast to the ERSPC trial, however, our study population reflects a referral population rather than a screening population; this fact may limit the generalizability of our results to some extent.

One objective of our study was to determine differences in cancer characteristics between the higher and the lower PSA group. In our series and in others, between 11 and 27% of PCAs with a PSA value between 2.5 and 4 ng/ml are high grade (Gleason score ≥ 7) [13–15]. Therefore, there is no PSA threshold able to differentiate between clinically significant and insignificant PCAs with both high sensitivity and high specificity [11, 13, 15]. In our retrospective analysis, men with a PSA between 2.5 and 4 ng/ml had a statistically significantly decreased risk of being diagnosed with high-grade PCA compared to men with a PSA of 4–10 ng/ml. However, men in the lower PSA group were also more likely to have potentially insignificant tumors.

Our results confirm that in lower PSA ranges PCAs with more favorable pathological features (i.e. Gleason

score ≤ 6 , less cancer volume in biopsy cores) are diagnosed, which is in line with published data [1, 2, 15–17]. In a recently published study, Makarov et al. [15] found more favorable pathological parameters among men who underwent radical prostatectomy at low PSA (2.5–4 ng/ml) compared to men with a PSA between 4 and 6 ng/ml. However, in the same study a trend towards improved recurrence-free survival for the low PSA group did not reach statistical significance in a total of more than 1,500 patients. So far there is no convincing evidence in the literature that lowering the PSA threshold for biopsy to <4 ng/ml will lead to an increased biochemical recurrence-free survival rate or even a better cancer-specific survival rate.

Moreover, there is concern that lowering the PSA threshold for prostate biopsy will lead to overtreatment of PCA patients. After lowering the PSA threshold at our institution, we identified more patients harboring potentially insignificant PCAs. Even though expectant management is an acknowledged treatment option for these patients, once a PCA is detected, many of them will opt for immediate curative treatment [18–20]. Additionally, in patients who subsequently underwent radical prostatectomy, final pathology revealed no significant differences between the two groups with regard to high Gleason scores, extraprostatic disease or positive surgical margins.

In contrast to most other studies which evaluated the performance of a PSA threshold <4 ng/ml, we primarily analyzed patients who underwent biopsy, not patients who underwent radical prostatectomy. We looked only at patients with a PSA between 2.5 and 10 ng/ml and a non-suspicious rectal examination. In this cohort we found the absolute risk difference of being diagnosed with high-grade PCA only to be 1% between a PSA threshold of 2.5 versus 4 ng/ml. This absolute risk difference implies that, compared with the lower PSA threshold, 100 men need to undergo prostate biopsy in order to find 1 additional patient with high-grade disease. The majority of patients

with high-grade PCA (Gleason score ≥ 7) are still amenable to curative treatment at a PSA level of 4 ng/ml. It is therefore conceivable that the number of men needed to biopsied at a PSA level of 2.5 ng/ml in order to find 1 patient that would lose the opportunity for cure by waiting for the PSA to rise to 4 ng/ml is still considerably higher than 100. These facts make us believe that lowering the PSA threshold for prostate biopsy from 4 to 2.5 ng/ml is not justified.

Our study has several limitations. No data concerning tumor volume in the prostatectomy specimens were available to determine potentially insignificant or unimportant PCAs according to Epstein et al. [21] or Ohori et al. [22] and to confirm the pretreatment criteria predictive of small insignificant PCA. In addition, pretreatment criteria, especially Gleason grading, were not available for all patients due to either small tumor volume in the biopsy cores or incomplete pathology reports. However, the pretreatment criteria predictive of small volume PCA were confirmed prospectively by Carter et al. [9] and are an accepted instrument to predict the presence of such tumors. We did not choose more contemporary nomograms like from Nakanishi et al. [23] or Steyerberg et al. [24] to predict indolent or potentially insignificant PCA because data on tumor length in biopsy cores were lacking very frequently. However, so far no consensus has been reached which criteria should be applied to reliably predict clinically insignificant or indolent cancer. Furthermore, we do not present follow-up data of treated patients. Therefore, no statement concerning progression-free survival rates for the two different PSA threshold values is possible. The absolute number of detected and subsequently treated PCAs is rather small, especially the absolute numbers for Gleason score ≥ 7 PCA and potentially insignificant cancers. Therefore, our results could be underpowered to detect statistically significant differences in tumor characteristics in the prostatectomy specimens between the two PSA groups. However, our analy-

sis is based on 506 men undergoing 798 prostate biopsies and we doubt that differences we were not able to detect are clinically important. A further potential confounding factor of the results is the lack that additional parameters such as a family history or PSA kinetics were not taken into account for biopsy decision-making. Recent evidence suggests that PSA velocity adds important information to identify high-risk PCA already in the pretreatment setting [25]. Hence, a recently published survey confirmed that more than 50% of surveyed urologists consider PSA velocity an important parameter to indicate a prostate biopsy [26].

We are well aware that the presented data will not settle the dispute over the optimal PSA threshold for prostate biopsy. Proponents of lower PSA thresholds might argue that as long as otherwise healthy men are dying from PCA, there is no overtreatment and that any number of biopsies is justified in order to detect more PCA at a potentially curable stage [27]. Based on our results, however, we do not support the notion that simply lowering the PSA threshold for biopsy < 4 ng/ml will lead to the detection of a significant amount of curable cancers which would be incurable at a PSA of 4 ng/ml. Hopefully, in the future, additional markers and further parameters like PSA velocity will potentially lead to a more tailored use of prostate biopsies and will ideally improve the diagnostic yield of this invasive test.

Conclusion

Lowering the PSA threshold for prostate biopsy from 4 to 2.5 ng/ml results in a substantial increase in the number of men who undergo biopsy and may result in an increased detection of potentially insignificant cancers. If total PSA alone is used to determine the need for prostate biopsy, the disadvantages of this lower threshold probably outweigh its potential benefits.

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